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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte XUEDONG SONG

Appeal 2009-007449
Application 10/718,989
Technology Center 1600

Decided: May 6, 2010

Before ERIC GRIMES, LORA M. GREEN, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's rejection of claims 64-85 and 89-92. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claim 64 is representative of the claims on appeal, and reads as follows:

64. A method for detecting an analyte within a test sample, the method comprising:

i) providing a lateral flow assay device that comprises a porous membrane in fluid communication with phosphorescent particles conjugated with a specific binding member, the phosphorescent particles comprising a phosphorescent label encapsulated within a matrix, the phosphorescent label emitting a detection signal having an emission lifetime of about 1 microsecond or more following excitation of the phosphorescent label and having a Stokes shift of greater than about 100 nanometers, wherein the porous membrane defines a detection zone within which is immobilized a capture reagent;

ii) contacting the lateral flow assay device with the test sample;

iii) subjecting the detection zone to illumination pulses to generate the detection signal; and

iv) thereafter, measuring the intensity of the detection signal, wherein the amount of the analyte within the test sample is proportional to the intensity of the detection signal.

The Examiner relies on the following evidence:

Jou	US 5,670,381	Sept. 23, 1997
Zarling	US 5,674,698	Oct. 7, 1997
Daniels	US 2002/0004246 A1	Jan. 10, 2002
Klimant	US 6,770,220 B1	Aug. 3, 2004
Rylatt	WO 97/09620	Mar. 13, 1997

O'Riordan et al., *Monofunctional Derivatives of Coproporphyrins for Phosphorescent Labeling of Proteins and Binding Assays*, 290 ANAL. BIOCHEM. 366-375 (2001).

The following grounds of rejection are before us for review:

I. Claims 64-77, 79, 80, and 82-84 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels, Klimant, and O'Riordan.

II. Claims 78 and 81 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels and Klimant, as further combined with Zarling.

III. Claims 85 and 89-91 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels and Klimant, as further combined with Rylatt.

IV. Claim 92 stands rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels, Klimant, and Rylatt, as further combined with Jou.

We affirm all of the above rejections.

ISSUE

Has the Examiner established by a preponderance of the evidence that the ordinary artisan would have a reason to combine the references to arrive at the claimed assay method?

FINDINGS OF FACT

FF1 According to the Specification:

> [T]he present invention is directed to a lateral flow, membrane-based assay device for detecting the presence or quantity of an analyte residing in a test sample. The device utilizes

> phosphorescence to detect the signals generated by excited phosphorescent labels. The labels may have a long emission lifetime so that background interference from many sources, such as scattered light and autofluorescence, is practically eliminated during detection. In addition, the phosphorescent labels may be encapsulated within particles to shield the labels from quenchers, such as oxygen or water, which might disrupt the phosphorescent signal.

(Spec. 5.)

FF2 The Examiner rejects claims 64-77, 79, 80, and 82-84 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels, Klimant, and O'Riordan.[1] (Ans. 4.) As Appellant does not argue the claims separately, we focus our analysis on claim 64, and claims 65-77, 79, 80, and 82-84 stand or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii).

FF3 The Examiner finds that Daniels teaches a method of detecting an analyte that meets all of the claimed limitations, except that Daniels teaches the use of semiconductor nanocrystals (luminescent or phosphorescent particles) conjugated to the specific binding member. (Ans. 4.)

FF4 Specifically, Daniels "relates to immunochromatographic test strips that use semiconductor nanocrystals as a detectable label." (Daniels, ¶2.)

FF5 Daniels notes:

> The general principle underlying test strip assays is that a ligand bound by a visually detectable solid support can be measured qualitatively (and in some cases semi-quantitatively).

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[1] The Examiner relies on O'Riordan as evidence that the luminescent/phosphorescent labels of Klimant would have an emission lifetime of about 1 microsecond or more, and a Stokes shift of 100nm or more. (Ans. 15.) Thus, we focus our analysis on the combination of Daniels and Klimant.

> Thus, while test strips may employ any one of a variety of assay schemes, including sandwich assays (both direct and indirect) and competitive reaction assays, all have in common the element of a detectable label that permits identification of an analyte of interest when present in an experimental sample.

(*Id.* at ¶5.)

FF6 Daniels also discusses that radiolabels, enzymes, metal sol, and fluorescent molecules have all been used as detectable labels. (*Id.* at ¶¶6-10.)

FF7 As to the use of fluorescent molecules, Daniels notes that different colored dyes may have different excitation wavelengths, and thus "the simultaneous use of two or more fluorescent tags with different excitation wavelengths requires multiple excitation light sources." (*Id.* at ¶11.)

FF8 Thus, Daniels teaches the use of semiconductor nanocrystals allows for the detection of one or more analytes in a single reaction. (*Id.* at ¶17.)

FF9 The Examiner notes that Daniels fails to teach "that the luminescent/phosphorescent particle comprises a phosphorescent label encapsulated within a matrix and that the label has an emission lifetime of about 1 microsecond or more and a Stokes shift of greater than about 100 nanometers." (Ans. 5.)

FF10 The Examiner relies on Klimant for teaching "the production and use of luminescent microparticles wherein long-lived phosphorescent labels are incorporated (encapsulated) within solid particles for use . . . as markers for labeling and detecting biomolecules." (*Id.*)

FF11 Specifically, Klimant teaches "luminescent micro- and nanoparticles with long-lived luminescence." (Klimant, col. 1, ll. 4-6.) Klimant teaches

that the particles may be used as "markers for labeling and detecting biomolecules." (*Id.* at col. 1, ll. 8-9.)

FF12 According to Klimant, "[l]uminescence measurement is a very common method in biological and chemical analysis . . . due to its high sensitivity, [and] versatility . . . . " (*Id.* at col. 1, ll. 30-33.)

FF13 Klimant also teaches that time-resolved luminescence allows one to separate by time the delayed measurement signal from the short-lived background fluorescence. (*Id.* at col. 2, ll. 7-10.)

FF14 The Examiner concludes that it would have been obvious to use the luminescent particles of Klimant in the assay method of Daniels because Klimant teaches the benefit of such luminescent particles, such as "the microparticles create long-lived luminescence, wherein the matrices eliminate or greatly reduce phosphorescence signal quenching by interfering oxygen that is common during luminescent measurement." (Ans. 5.)

FF15 The Examiner rejects claims 78 and 81 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels and Klimant, as further combined with Zarling. (*Id.* at 8.)

FF16 The Examiner relies on the combination of Klimant and Daniels as set forth above. (*Id.*)

FF17 The Examiner notes that the combination fails to teach "that the detection signal is measured from 1 to 100 microseconds after the detection zone is subjected to one or more pulses of illumination, or that the signal is measured by a time-gated detector." (*Id.*)

FF18 The Examiner relies on Zarling for teaching the use of "up-converting and down-converting phosphorescent/luminescent reporters for use in biological assays using laser excitation techniques." (*Id.*)

FF19 The Examiner finds that Zarling teaches that "[v]arious means can be used for detection of the phosphorescent emission(s), including a time-gated and/or frequency-gated light detector for rejection of residual background noise." (*Id.*) The Examiner finds further that Zarling teaches that a pulsed-excitation source is preferably used with a time-gated detector. (*Id.*)

FF20 Zarling teaches that any convenient light source and any convenient detector may be used to detect the label. (Zarling, col. 5, ll. 54-63.) Zarling teaches that detection of multiple reporters is possible, and that time multiplexing, or time-gating techniques, wherein only one reporter is emitting at a time, may be used. (*Id.* at col. 6, ll. 4-34.) Zarling teaches further that pulsed excitation with time-gated detection when a label having a long-lived emission is used allows for rejection of background fluorescence and phosphorescence. (*Id.* at col. 32, l. 49-col. 33, l. 12.)

FF21 The Examiner concludes that it would have been obvious to the ordinary artisan at the time of invention to use a pulsed excitation source with time-gated excitation as taught by Zarling in the lateral flow assay taught by the combination of Daniels and Klimant because the use of such methods "provides a method of recording long-lived emission after termination of illumination, wherein signal(s) attributable to phosphorescence is recorded, while short-lived autofluorescence and scattered illumination light is rejected." (Ans. 9.)

FF22 The Examiner rejects claims 85 and 89-91 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels and Klimant, as further combined with Rylatt. (*Id.*)

FF23 The Examiner relies on the teachings of Daniels and Klimant as set forth above. (*Id.*)

FF24 The Examiner notes that Daniels teaches the use of an additional control line or regions, but fails to teach its use as a calibration zone. (*Id.*) The Examiner also notes that Klimant also fails to teach the use of a calibration zone. (*Id.*)

FF25 The Examiner relies on Rylatt for teaching a lateral flow assay device that contains calibration zone(s) as well as a test (detection) zone. (*Id.*; *see also id.* at 9-10 for a discussion of the calibration zone of Rylatt.)

FF26 The Examiner concludes that it would have been obvious to the ordinary artisan to include a calibration zone as taught by Rylatt in the lateral flow assay device taught by the combination of Daniels and Klimant as the calibration zone allows for "accurate quantitative determination of a target analyte in a test sample, because the signal produced in the calibration zone is utilized to calibrate the signal produced in the test zone." (Ans. 10-11.)

FF27 The Examiner rejects claim 92 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels, Klimant, and Rylatt, as further combined with Jou. (Ans. 11.)

FF28 The Examiner relies on the teachings of Daniels, Klimant, and Rylatt as set forth above. (*Id.*) The Examiner notes that the references as

combined "fail to teach that the capture reagent included in the calibration zone comprises a polyelectrolyte." (*Id.*)

FF29 The Examiner finds that Jou teaches "a device for performing an assay comprising a porous material containing a capture or reaction zone with an immobilized capture reagent." (*Id.*)

FF30 The Examiner further finds that Jou teaches the use of a cationic or anionic polymeric substance (polyelectrolyte) as the capture reagent, "which enables the production of a generic solid phase device for use in specific binding assays." (*Id.*)

FF31 Specifically, Jou teaches that a binding member for an analyte of interest is conjugated to a first charged substance, wherein a reaction zone containing a second immobilized substance that is oppositely charged to the first charged substance is used to immobilize the specific binding complex. (Jou, col. 6, ll. 26-37.)

FF32 Jou teaches that assay may be a sandwich assay, a competitive assay, or an indirect assay. (*Id.* at col. 6, ll. 42-47.)

FF33 Jou also teaches the use of a label to detect the specific binding complex, wherein the label may include chromogens, catalysts, fluorescent compounds, chemiluminescent compounds, enzymes, dye particles, etc. (*Id.* at col. 8, l. 66-col. 9, l. 9.)

FF34 The Examiner thus concludes that it would have been obvious to the ordinary artisan at the time of invention to use a polyelectrolyte as the capture reagent in the calibration zone as taught by Jou in the lateral flow assay device taught by the combination of Daniels, Klimant, and Rylatt

because the use of such a capture reagent allows for the production of a generic solid phase device. (Ans. 12.)

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *see also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. Moreover, an "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982).

ANALYSIS

Appellant asserts that the ordinary artisan would not have combined Klimant with Daniels to arrive at the claimed invention. (App. Br. 6.) Appellant asserts further that the Examiner relies on the equivalence of the

semiconductor nanocrystals of Daniels to the luminescent particles of Klimant because "both particles provide detectable luminescent/phosphorescent signals, can be conjugated to biomolecules and can be effectively used as markers for labeling and detecting biomolecules," to make the combination. (*Id.* at 8.) Appellant argues that finding is in error, arguing that the fluorescent semiconductor nanoparticles of Daniels are not functionally, nor mechanically, equivalent to the phosphorescent particles of Klimant. (*Id.* at 9.) According to Appellant, "the two different materials provide very different types of luminescent signals." (*Id.*; *see also id.* at 9-11 for a discussion of the differences between the signals.) Appellant asserts further that the structures of the two materials are different, as the particle structures of Klimant use polyacrylonitrile or its copolymers to encapsulate the phosphorescent molecules, and that the phosphorescent molecules could not be in a crystal as taught by Daniels, or even in an aggregate, as the phosphorescence would be quenched. (*Id.* at 10-11.)

Appellant also asserts that the Examiner relied on improper hindsight in combining the references to arrive at the claimed invention. (App. Br. 16.) According to Appellant, "[n]o common sense line of reasoning has been provided" to combine the references as suggested by the Examiner to arrive at the claimed invention. (*Id.* at 17.)

Appellant argues further the references teach away from the combination. (*Id.* at 11.) According to Appellant, the emission spectra of the nanocrystals of Daniels are narrow, symmetric, Gaussian, or mostly Gaussian, without a tailing region, and thus solve problems that may be encountered with other luminescent materials that may display spectral

overlap, due, in part, to overlap in the spectra near the tailing region. (*Id.* at 11-12.) Klimant, Appellant argues, "utilizes phosphorescent particles that take advantage of the phosphorescence time delay of the phosphorescent particles," and thus "the emission spectra are neither symmetrical nor Gaussian." (*Id.* at 12.) Appellant thus asserts that the "two types of detection regimes utilized by the references are fundamentally different." (*Id.* at 13.)

Appellant argues further that to modify Daniels as suggested by the Examiner would render Daniels unsatisfactory for its intended purpose. (*Id.* at 14.) Appellant asserts, as already noted, Daniels teaches that the emission spectra of the nanocrystals of Daniels are narrow, allowing for detection of multiple analytes. (*Id.*) According to Appellant, "[i]f the emission spectrum of the labeling particle is not narrow, it is not practical to achieve simultaneous detection of multiple analytes . . . because of the likely fluorescence overlap of one particle with other signals." (*Id.*) The phosphorescent particles of Klimant, Appellant argues, have long luminescent decay times, and if substituted for the nanoparticles of Daniels, "not only could the emission spectra of different particles overlap, but also the detection system of [Daniels] will not work optimally because the emission signal of the phosphorescent particles of [Klimant] is more effectively separated from the other unwanted backgrounds through lifetime difference, rather than wavelength difference." (*Id.* at 15.) Specifically, Appellant asserts, "two totally different detection techniques are desired for effectively detecting the two types of particles." (*Id.*)

Appellant's arguments are not convincing. Daniels establishes that the claimed assay method using a lateral flow assay device is known. Klimant establishes that the claimed labels, that is, "phosphorescent particles comprising a phosphorescent label encapsulated within a matrix, the phosphorescent label emitting a detection signal having an emission lifetime of about 1 microsecond or more following excitation of the phosphorescent label and having a Stokes shift of greater than about 100 nanometers," are also known. Thus we agree with the Examiner that it would have been obvious to the ordinary artisan to use the phosphorescent labels of Klimant, which Klimant specifically teaches may be used as markers for labeling and detecting biomolecules.

We have considered Appellant's arguments regarding the technical differences between the nanocrystal label of Daniels and the phosphorescent particle of Klimant. But as established by the Court in *KSR*, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. at 421. Thus, the ordinary artisan would understand what reagents and apparatus would be required to measure the label being used in the assay. In addition, as evidenced by Daniels, labels such as radioactive labels, enzymes labels, fluorescent compounds, etc., which are all labels having very different structures, different measurement methods, etc., are all known in the art to be useful as labels for detecting biomolecules in specific binding assays.

As to Appellant's argument that substituting the label of Klimant for the nanocrystal of Daniels would destroy the purpose of Daniels as the labels of Daniels allow for the detection of more than one analyte, Daniels teaches

the detection of one or more analytes, and thus the purpose of Daniels is the detection of an analyte, and substituting the phosphorescent particle of Klimant for the nanocrystal of Daniels would still allow the ordinary artisan to achieve the purpose of Daniels, that is detection of an analyte. Moreover, Daniels does not teach that fluorescent labels cannot be used to detect more than one analyte, but only that such labels may have different excitation wavelengths, and thus may requires multiple excitation light sources. As already noted, the ordinary artisan would understand what reagents and apparatus are required for the detection of different labels, and would be able to balance each of the label's positives and negatives to determine which label would best suit their particular needs. We conclude that the combination of Daniels and Klimant is a combination of familiar elements according to known methods, and would yield predictable results, and we thus agree with the Examiner that the combination renders the method of claim 64 obvious.

As to the rejection over Daniels and Klimant, as further combined with Zarling, Appellant argues that the labels of Zarling are up-converting labels, capable of multiphoton excitation, and thus "the excitation and emission detection regimes must be specific for these materials." (App. Br. 17-18.) Appellant asserts that Zarling does not disclose the use of the materials in a dry chemistry based system, such as a lateral flow system. (*Id.* at 18.) Appellant asserts further that the Examiner "has parsed and dissected only certain portions of [Zarling], and then used these dissected portions in a way that would require a substantial reconstruction of [Daniels], which is improper under 35 U.S.C. § 103." (*Id.* at 19.) Thus, Appellant argues, the

Examiner has engaged in improper hindsight in combining the references to arrive at the claimed invention. (*Id.* at 20.)

Claim 78 is drawn to the method of claim 64, wherein the detection zone is subjected to one or more pulses of illumination, and claim 81 is drawn to the method of claim 64, wherein the detection signal is measured by a time-gated detector. Zarling is not relied on for its teaching of an up-converting label, but for its teaching that the use of pulsed excitation with time-gated detection when a label having a long-lived emission is used allows for rejection of background fluorescence and phosphorescence. As the emission of the labels of Klimant is long-lived, the ordinary artisan would understand that using pulsed excitation with time-gated detection in the detection of the labels of Klimant would provide the same advantage.

As to the rejection of claims 85 and 89-91 over the combination of Daniels, Klimant, and Rylatt, Appellant reiterates the argument made as to independent claim 64. (App. Br. 20.) Those arguments are not found to be convincing for the reasons set forth above with respect to claim 64.

As to the rejection of claim 92 over the combination of Daniels, Klimant, Rylatt, and Jou, Appellant argues that the proposed modification of Daniels would render Daniels unsuitable for its stated purpose. (App. Br. 22.) Jou teaches, Appellant asserts, the formation of a sandwich comprising the analyte of interest, wherein a second charged substance is used to enhance the immobilization of the sandwich on the membrane. (*Id.* at 22-23.) According to Appellant, if an immobilized component of Daniels or Rylatt were to be replaced by the second charged substance of Jou, the device would not function, as it would result in the loss of the desired

specific binding capability. (*Id.* at 23-24.) Appellant asserts that "the only teaching directed toward utilization of a polyelectrolyte as a capture reagent in a calibration zone is in the [instant] application," and thus the Examiner has engaged in improper hindsight to combine the references to arrive at the claimed invention. (*Id.* at 25-26.)

Again, Appellant's arguments are not convincing. Jou teaches that a charged molecule that has a charge opposite to that of the polyelectrolyte capture reagent is attached to the specific binding members, thus the specific binding capability of the assay is not lost. As set forth by the Examiner, the ordinary artisan would have used a calibration capture reagent comprising a polyelectrolyte as taught by Jou in order to obtain the advantages of such as taught by Jou, such as the use of such a capture reagent allows for the production of a generic solid phase device.

CONCLUSION OF LAW

We conclude that the Examiner established by a preponderance of the evidence that the ordinary artisan would have a reason to combine the references to arrive at the claimed assay method.

We thus affirm the rejection of claims 64-77, 79, 80, and 82-84 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels, Klimant, and O'Riordan; the rejection of claims 78 and 81 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels and Klimant, as further combined with Zarling; the rejection of claims 85 and 89-91 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels and Klimant, as further combined with Rylatt; and

the rejection of claim 92 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Daniels, Klimant, and Rylatt, as further combined with Jou.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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